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Joseph Monforte

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EXAMINER

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.

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Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|---|--|
| Office Action Summary | Application No. 10/622,010 | Applicant(s) MONFORTE, JOSEPH | |
| | Examiner Young J. Kim | Art Unit 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 and 24-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 and 24-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The present Office Action is responsive to the Amendment received on March 30, 2006¹.

Preliminary Remark

Claim 23 is canceled.

Claims 1-22 and 24-50 are pending and are under prosecution herein.

Claim Objections

The objection of claim 47 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, made in the Office Action mailed on August 22, 2005 is withdrawn in view of the Amendment received on March 30, 2006.

Claim Rejections - 35 USC § 112

The rejection of claims 1-50 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on August 22, 2005 is withdrawn in view of the Amendment received on March 30, 2006, and in careful reconsideration of the application.

Claim Rejections - 35 USC § 102 - Maintained

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

¹ The Amendment received on January 4, 2006 and March 30, 2006 is collectively termed, "Amendment received on March 30, 2006."

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The rejection of claims 25-27, 33, 34, 37-45, and 50 under 35 U.S.C. 102(e) as being anticipated by Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000), made in the Office Action mailed on August 22, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on March 30, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Preliminarily, claims 26, 27, 33, 34, 37-45, and 50 are multiple dependent claims, depending directly or indirectly from independent claims 1 and 25. The rejection of claims under this section is based on their dependency on claim 25.

Dooley et al. disclose a method of quantitating a plurality of expression products from a plurality of biological samples, the method comprising:

- a) providing at least one informative nucleic acid array, wherein said informative nucleic acid array is created by immobilizing nucleic acids corresponding to differentially expressed RNAs in a biological sample (thus selective) (column 10, line 8; column 3, lines 36-38 (informative arrays); column 5, lines 17-19);
- b) hybridizing a plurality of defined sequence probes which are labeled (column 10, lines 7-9; column 8, line 41); and
- c) detecting hybridization to each of the plurality of defined sequence probes (Figure 1, steps IV and V), thereby anticipating claim 25.

With regard to claims 26 and 27, Dooley et al. disclose that the nucleic acids immobilized on the informative array are produced via amplification, specifically PCR (column 8, lines 50-54).

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The amplification of the differentially expressed RNAs for arraying them on the informative array would necessarily involve two or more target specific amplification reaction and spatial arraying of the amplified product in two or more locations on the array as the array comprises more than one detection spot, anticipating claims 33-34.

With regard to claim 37, Dooley et al. disclose that informative nucleic acid array is employed in identifying disease related genes (column 10, lines 45-57).

With regard to claims 38 and 39, Dooley et al. disclose that the array is a two-dimensional array (column 7, lines 43-44).

With regard to claims 40 and 41, Dooley et al. disclose that the nucleic acid can be arrayed on beads (column 7, lines 50-53; column 4, lines 14-15), as well as stating that “[o]ther platforms may be used, as desired.

With regard to claim 42, the array surface, in an embodiment, is disclosed as being glass (column 7, line 43), plastic (column 7, line 46), or silicon (column 8, line 33).

With regard to claim 43, the nucleic acid probes derived from cells, such as that which is generated from RNA (column 8, lines 39-42; column 9, line 22) or cDNA (column 9, line 5) is hybridized to the informative array.

With regard to claim 44, the nucleic acid probe is disclosed as being fluorescently labeled (column 8, line 41).

With regard to claim 45, claim 45 does not require that the method employ an amplifiable signal element be oligonucleotide, but rather further defines the Markush claim from which a detectable signal can be selected from. Since Dooley et al. disclose one of the Markush members (fluorescent label), claim limitation is met.

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With regard to claim 50, Dooley et al. disclose comparison of the detected hybridization between samples (column 4, lines 24-28; Figure 1, steps I-III in view of V).

Therefore, Dooley et al. anticipate the invention as claimed.

Response to Arguments:

Applicants' statement regarding the actual invention is appreciated. However, it is noted that the presently rejected claims are anticipated by Dooley et al. for the following reasons.

According to MPEP 2106(II)(C), claims are to be given their broadest reasonable interpretation:

"Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Limitations appearing in the specification but not recited in the claim are not read into the claim. > E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily). < In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.").

A step-by-step claim interpretation of claim 25 is discussed below:

Step A:

"Providing at least one nucleic acid array comprising a plurality of amplified nucleic acids corresponding to a plurality of expressed RNA samples, each obtained from a biological sample, which amplified nucleic acids are produced by selective amplification of the plurality of expressed RNA samples."

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Interpretation:

The nucleic acid that is provided must comprise a plurality of amplified nucleic acids which resemble a plurality of expressed RNA samples. The word, “corresponding” does not necessarily require that the actual RNA samples be comprised by the nucleic acid array, but rather, that the nucleic acid array comprise a plurality of amplified nucleic acid that has something to do with the expressed RNA samples (i.e., cDNA, portions of the RNA, etc.)

In addition, the limitation which recites that the amplified nucleic acids are produced by “selective amplification” of the plurality of expressed RNA sample, does not have any special meaning attributed since the claims do not recite what the selected criteria is. In its largest breadth, nucleic acids of all expressed RNA could be embraced by this language, since selection criteria could be that all expressed RNA be amplified.

Dooley et al. disclose an array, which is disclosed as an informative array, wherein the informative array comprises nucleic acid sequences which are derived from (i.e., corresponding to) differentially expressed RNAs (column 3, lines 27-38). These nucleic acid sequences are disclosed as being “PCR-amplification products” (column 8, lines 48-54).

Thus reading the reference as a whole, clearly indicates that the informative array comprises a plurality of nucleic acid sequences correspond to differentially expressed RNA molecules, said plurality of nucleic acid sequences which are “arrayed” onto the surface of said informative array are PCR amplified, meeting all of the limitation of claim 25 step a). Since differentially expressed RNA molecules must be PCR amplified for their immobilizing, the amplification would necessarily be selective.

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Step B:

“Hybridizing a plurality of defined sequence probes, which defined probes each comprise a different polynucleotide sequence, and which probes are each capable of generating different detectable signal, to the nucleic acid array”

Interpretation:

It appears that Applicants are reading more meaning to the limitation, “a plurality of defined sequence probes,” than it really requires in the claims. Applicants’ position is that the claimed plurality of defined sequence probes are different from those which are employed by Dooley et al. because the plurality of probes employed by Dooley et al. are “uncharacterized heterogenous pool of labeled cDNA derived from the biological RNA sample,” while the probes of the, “present specification are the labeled defined sequence nucleic acid molecules that are used to interrogate the biological sample nucleic acids that are affixed to the array.” (page 15, bottom paragraph, Response).

It is maintained that Dooley et al. hybridize a pool of labeled cDNA derived from the biological sample, however, these labeled cDNAs have a “defined” sequence, each of these sequences of which detectable upon hybridization of the informative array, thereby clearly meeting the limitation.

Step C:

Detecting hybridization of each of the plurality of defined sequence probes.

Interpretation:

Dooley et al. clearly detects the presence of the labeled, hybridized probes, thereby meeting this limitation.

For the reasons set forth above, Dooley et al. clearly anticipate the invention as claimed and the rejection is maintained.

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Claim Rejections - 35 USC § 103

The rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000) in view of Lockhart et al. (WO 97/10365, published March 20, 1997), made in the Office Action mailed on August 22, 2005 is withdrawn in view of the Amendment received on March 30, 2006, canceling the rejected claim.

Rejection, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1-13, 15-22, 24, 26, 27, 30-45, and 47-50 under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000) in view of Lockhart et al. (WO 97/10365, published March 20, 1997), made in the Office Action mailed on August 22, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on March 30, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

Preliminarily, claims 26, 27, 30-45, and 50 are multiple dependent claims, depending directly or indirectly from independent claims 1 and 25. The rejection of claims under this section is based on their dependency on claim 1.

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The Rejection:

Dooley et al. disclose a method of screening a candidate compound to identify a compound with a physiological effect on a biological sample, the method comprising the steps:

- a) contacting a biological sample with a candidate compound (minoxidil, column 10, lines 1-4);
- b) obtaining expressed RNAs from the sample (column 10, lines 4-5);
- c) arraying a plurality of nucleic acids corresponding to the plurality of expressed RNAs from the sample (column 10, line 8; column 3, lines 36-38 (informative arrays); column 5, lines 17-19);
- d) hybridizing a plurality of sequence probes derived from a sample treated with a candidate compound, so as to find other compounds that produce a similar biomarker response (column 10, lines 7-9);
- e) quantitating and detecting the hybridization signal, thereby identifying a compound that exerts a physiological effect on a biological sample (Figure 1, steps IV and V).

With regard to entering the quantitated hybridization signal into a database, the method of Dooley et al. compares the hybridization signal, which would necessarily require the entering of the hybridization signal into a computer which correlates the identified biomarkers with their expression level which is a database in its form (column 11, lines 7-21).

With regard to claim 3, Dooley et al. disclose employing control hybridization signal produced from the informative array (Figure 1, step III in view of Step V).

With regard to claim 12, Dooley et al. employ cell culture (Figure 1, step I; column 5, lines 34-35) and tissue (column 5, lines 32-33) as samples.

With regard to claim 13, Dooley et al. employ cell lines (column 5, line 34) as samples.

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With regard to claims 15 and 16, Dooley et al. disclose that the samples are of eukaryotic (i.e., human or mammalian, column 4, lines 59) as well as *unicellular organisms*, plants, protests, and fungi (column 4, lines 60-64).

With regard to claims 4, 23, 24, 26, 27, 33, and 34, Dooley et al. disclose that the informative arrays are arrayed with isolated or purified immobilized nucleic acids, either native or synthetically created sequences, including PCR-amplification products (column 8, lines 48-54), such as oligonucleotide fragments, partial and full-length cDNA, expressed sequence tags (ESTs), including both partial and full-length ESTs, as well as RNA, DNA, or PNA (column 5, lines 1-9).

With regard to claim 37, Dooley et al. disclose that informative nucleic acid array is employed in identifying disease related genes (column 10, lines 45-57).

With regard to claims 38 and 39, Dooley et al. disclose that the array is a two-dimensional array (column 7, lines 43-44).

With regard to claims 40 and 41, Dooley et al. disclose that the nucleic acid can be arrayed on beads (column 7, lines 50-53; column 4, lines 14-15), as well as stating that “[o]ther platforms may be used, as desired.

With regard to claim 42, the array surface, in an embodiment, is disclosed as being glass (column 7, line 43), plastic (column 7, line 46), or silicon (column 8, line 33).

With regard to claim 43, the nucleic acid probes derived from cells, such as that which is generated from RNA (column 8, lines 39-42; column 9, line 22) or cDNA (column 9, line 5) is hybridized to the informative array.

With regard to claim 44, the nucleic acid probe is disclosed as being fluorescently labeled (column 8, line 41).

With regard to claim 45, claim 45 does not require that the method employ an amplifiable signal element be oligonucleotide, but rather further defines the Markush claim from which a detectable signal can be selected from. Since Dooley et al. disclose one of the Markush members (fluorescent label), claim limitations are met.

With regard to claim 50, Dooley et al. disclose comparison of the detected hybridization between samples (column 4, lines 24-28; Figure 1, steps I-III in view of V).

Dooley et al. do not employ their method for contacting a plurality of samples with a plurality of members of a compound library and generating an RNA sample from each of the plurality of the biological sample and arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce an array.

Dooley et al. do not disclose that each of the plurality of biological sample is contacted with a different member of the compound library (claim 2).

Dooley et al. do not explicitly disclose the use of control nucleic wherein the control biological sample comprises an untreated biological sample or a 0 time point sample (claim 5).

Dooley et al. do not explicitly disclose the step of quantitating hybridization signal wherein the signal differs qualitatively or quantitatively (claim 6), increased or decreased (claim 7), relative to the control hybridization signals.

Dooley et al. do not explicitly disclose the detection of the quantitated hybridization signals that differ from a control hybridization signal by performing at least one statistical analysis (claim 8), wherein the signal is increased or decreased at least one standard deviation (claim 9), at least two standard deviation (claim 10).

Dooley et al. do not explicitly disclose a method of using a plurality of nucleic acid arrays (claim 11).

Dooley et al. do not explicitly disclose a method comprising obtaining expressed RNA samples from at least 500 biological samples (claim 18), at least 1000 biological samples (claim 19), at least 10,000 biological samples (claim 20), each of which biological samples is treated with a different member of a compound library.

Dooley et al. do not explicitly disclose obtaining one or more expressed RNA samples by isolating total cellular RNA (claim 21).

Dooley et al. do not explicitly disclose obtaining one or more expressed RNA samples by isolating messenger RNA (claim 22).

Dooley et al. do not explicitly disclose pooling of amplification products for arraying (claim 30), wherein selective amplification amplifies between about 5 and about 100 polynucleotide sequences (claim 31), between about 10 and about 50 polynucleotide sequences (claim 32).

Dooley et al. do not disclose a method of employing housekeeping genes (claims 35 and 36).

Dooley et al. do not disclose a method of employing amplifiable signal element for detecting a plurality of defined sequence probes hybridized to the array (claim 46), involving chemiluminescent detection (claims 47-49).

With regard to claims 2 and 17, Lockhart et al. disclose a method of employing a microarray for screening a plurality of compounds for identifying a candidate drug (page 8, line 30 through page 9, line 4).

With regard to claim 5, the control sample comprises an untreated biological sample (page 9, lines 5-7).

With regard to claims 6 and 7, Locakhart et al. the identification of candidate drug by the screening process is achieved via comparison of the expression profile from a test and a normal sample (page 9, lines 4-9; page 53, lines 22-24).

With regard to claims 8-10, Lockhart et al. disclose a method of detecting the signal difference by performing at least one statistical analysis (pages 58-60), wherein the differential expression measured which would necessarily include at least one or two standard deviations (page 62 through page 66; page 17, lines 2-4).

With regard to claims 21 and 22, Lockhart et al. disclose explicitly the steps involved in generating a RNA expression product (involved in Dooley et al.) which involves the steps of isolating total RNA and mRNA (page 4, lines 26-28; page 28, lines 17-20).

With regard to claim 30, Lockhart et al. disclose pooling (page 7, lines 10-12).

With regard to claims 31 and 32, depending on the number of the differentially expressed RNAs identified by the method of Dooley et al., the selective amplification would necessarily amplify between about 5 to about 100; or between about 10 and about 50 polynucleotide sequences.

With regard to claim 35, Lockhart et al. disclose the use of housekeeping genes for internal expression control (page 17, line 5; page 35, line 25 to page 36, line 5).

With regard to claim 36, the differentially expressed nucleic acid produced by treatment with a particular compound will necessarily be different the differentially expressed nucleic acid produced from a different compound (thus different second defined sequence probe). The use of housekeeping genes (or the first defined sequence probe) as an expression control, as demonstrated by Lockhart et al. will be same sequence however.

With regard to claims 47-49, Lockhart et al. disclose a method of detection involving enzyme and substrate (or ligand) (page 31, lines 21-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Dooley et al. with the teachings of Lockhart et al. to arrive at the claimed invention for the following reasons.

Applicants describe a classical microarray configuration, which is disclosed as below:

“the classical microarray formats known in the art (*e.g.* Thomas *et al.*) typically involve the arrangement of large numbers (*e.g.*, hundreds or thousands) of defined “bait” sequences spatially arrayed on a solid phase surface, each in a unique addressable location, followed by application of a labeled nucleic acid sample (typically a collection of RNA or cDNA) to the microarray.” (page 17, 3rd paragraph).

Applicants state that in contrast to such configuration, the claimed invention uses a novel variation of the classical microarray configuration, wherein the novel approach “flips” the standard microarray paradigm in that the nucleic acid samples are fixed on the solid phase support and the nucleic acid probe of defined sequence in solution is hybridized thereto.

This point is not found persuasive for the following reasons.

Step (b) of claim 1 recites that an expressed RNA sample is obtained from a sample treated with a compound, and that in step (c), a plurality of nucleic acids *corresponding to* the plurality of expressed RNA samples are arrayed to produce a nucleic acid array.

Such array is disclosed by Dooley et al., wherein the artisans first conduct a differential expression using a “classical” array as described by the instant application. However, upon detecting the genes or the transcripts which are differentially expressed, those genes (or transcripts) are ranked and later arrayed on a solid surface in order to make what the artisans call, “informative array.” In at least one embodiment, Dooley et al. disclose a method of screening a plurality of compounds (such as drugs) in order to identify a candidate compound, wherein in that embodiment, a drug minoxidol

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is applied to a sample and its expression pattern is determined and compared against a control sample which had not been treated (*ut supra*). The differentially expressed genes (transcripts) were determined using the classical microarray containing a plurality of “bait” probes. However, the disclosure of Dooley et al. further takes the plurality of differentially expressed genes to make the informative array comprised of genes which are of particular interest. The informative array is then employed in testing a candidate compound by treating a sample with a candidate compound and detecting and comparing its expression pattern against the expression pattern produced from a control sample in order to determine whether the candidate compound is likely to produce a similar effect to that of, for example, minoxidol.

Dooley et al. disclose that the use of informative array provides the following advantages:

“It is another advantage of the present invention for informative arrays to increase the likelihood that the gene sequences immobilized on it will be more informative (e.g., differentially expressed) in a desired application, *relative to a general array lacking a similar level of informative potential.*” (column 4, lines 19-24)

“Further more, it is another technical advantage of the present invention for informative array to permit *reduction in the total number of gene sequences immobilized on the informative array.* A reduction in the size of the informative array, due to the exclusion of non-informative genes from the list of candidate genes during the gene selection process.” (column 4, lines 28-35).

Hence one of ordinary skill in the art at the time the invention was made would have been clearly motivated to employ the informative array of Dooley et al., that is an array produced by first identifying genes that are expressed based on a certain condition (such as treatment with a compound), wherein the identified genes are immobilized on the array, for the explicit advantage of increasing the likelihood that the gene sequences on the array will be more informative and that the

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array will permit reduction in the total number of gene sequences immobilized on the array. The reduction of in the total number of gene sequences immobilized on the array would have allowed one of ordinary skill in the art to clearly envision cost-effectiveness of conducting an experiment on such array.

With regard to the teachings provided by Lockhart et al., the use of control samples, wherein the control sample is explicitly disclosed as being untreated sample, the use of housekeeping genes in an array for the purpose of quality control, and detection of differentially expressed genes above a certain threshold (or standard deviation), are techniques commonly practiced in the art as the desire to control quality of the expression profiles, and setting threshold from which to detect differential expression of genes are common across methods involving array of immobilized oligonucleotide probes.

With regard to use of plurality of nucleic acid array (claim 11), one of ordinary skill in the art would have been motivated to employ a plurality of informative array of Dooley et al. for testing different candidate compound of a compound library.

With regard to claims 18-20, drawn to the number of samples from which to obtain RNA samples, would have been obvious in view of the fact that each compound of a compound library being test would have required a different sample.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that Dooley et al. do not describe the construction of an array where the material arrayed onto the solid support is uncharacterized material derived from a plurality of RNA samples or derivative products (page 18, 1st paragraph, Response).

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This argument is not found persuasive because neither does the claim recite that the RNA are uncharacterized.

In addition, the invention clearly contemplates an embodiment, wherein the nucleic acids on the array is characterized. If it were not so, claims 24, 26, 27, etc. would not require that the nucleic acids of the array are “selectively amplified” prior to their immobilized on the array. How can uncharacterized RNA be amplified “selectively” without first knowing its sequence?

Applicants contend that the claimed invention does not employ ranked differentially expressed gene sequences as bait on an array (page 18, 2nd paragraph, Response).

Applicants are reminded that the claims, as written, does not exclude this embodiment, and certainly embraces the embodiment disclosed by Dooley et al.

Next, Applicants contend that Dooley et al. do not disclose the step of arraying a plurality of nucleic acids corresponding to the plurality of RNA samples to produce a nucleic acid array (page 17, bottom paragraph; Response). Applicants state that while Dooley et al., on column 3, lines 36-38, disclose that the informative array of Dooley et al. places sequences derived from ranked differentially expressed genes on the informative array, the artisans do not describe a plurality of RNA samples (or material derived directly from the RNA samples, e.g., cDNA samples) assembled on an array (page 18, 3rd paragraph; Response).

This argument is confusing.

It would appear that Applicants’ appear to be stating that Dooley et al. do disclose an array which comprises a plurality of nucleic acids that are known to be differentially expressed (i.e., RNA expression). Are Applicants stating that the nucleic acid molecules immobilized on the informative array of Dooley et al. are not materials derived from RNA samples?

If this argument is assumed, then how does one of ordinary skill in the art interpret the below statement made by Dooley et al. found on column 8, beginning at line 49?

50 Numerous internal controls, both positive and negative, may be included on the nucleic acid array surface. The immobilized nucleic acid samples of specific gene sequences may be generated synthetically as oligonucleotides, PCR-amplification products, plasmids, or from other sources.

As it can clearly be seen, the immobilized nucleic acid samples of specific gene sequences may be generated synthetically (such as photolithography, e.g., Affymetrix®), or PCR-amplification products, plasmids, or from other sources.

If these specific gene sequences are PCR amplified, one of ordinary skill in the art would readily recognize that the source of the gene transcript would be required by well known process of RT-PCR. In addition, the field of microarray is replete with prior art which employ immobilizing PCR products on microarray surfaces (i.e., Pat Brown technology which immobilizes PCR products on solid surface by capillary reaction to produce a microarray).

With regard to Applicants' arguments drawn to defined probes, it appears that Applicants are reading more meaning to the limitation, "a plurality of defined sequence probes," than it is really required in the claims. Applicants' position is that the claimed plurality of defined sequence probes are different from those which are employed by Dooley et al. because the plurality of probes employed by Dooley et al. are "uncharacterized heterogenous pool of labeled cDNA derived from the biological RNA sample," while the probes of the, "present specification are the labeled defined sequence nucleic acid molecules that are used to interrogate the biological sample nucleic acids that are affixed to the array." (page 15, bottom paragraph, Response).

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It is maintained that Dooley et al. hybridize a pool of labeled cDNA derived from the biological sample, however, these labeled cDNAs have a “defined” sequence, each of these sequences of which detectable upon hybridization of the informative array, thereby clearly meeting the limitation.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000) in view of Lockhart et al. (WO 97/10365, published March 20, 1997) as applied to claims 1-13, 15-24, 26, 27, 30-45, and 47-50 above, and further in view of Cho et al. (PNAS, August 14, 2001, vol. 98, no. 17, pages 9819-9823), made in the Office Action mailed on August 22, 2005 is maintained for the reasons of record.

Applicants’ arguments presented in the Amendment received on March 30, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, “Response to Arguments” section.

The Rejection:

The teachings of Dooley et al. and Lockhart et al. have already been discussed above.

Dooley et al. and Lockhart et al. do not explicitly disclose treatment with members of the compound library recited in claim 14.

Cho et al. disclose a method involving treating a sample which overexpresses RI α gene with RI α antisense and determining the expression profile employing microarray (page 9819, 2nd column, 1st-3rd paragraph).

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Dooley et al. and Lockhart et al. with the teachings of Cho et al. to arrive at the claimed invention.

While Dooley et al. and Lockhart et al. are not explicit in what type of compound or drug can be screened so as to identify a candidate compound or drug, as evidenced by Cho et al., antisense is one of many well-known compound which potentially has therapeutic use in treatment of certain conditions. In the word of Cho et al., the artisans state:

“Antisense oligonucleotides can selectively block disease-causing genes, and cancer genes that have been chosen as potential targets for antisense drugs to treat cancer.” (Abstract)

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the teachings of Dooley et al. and Lockhart et al. for screening a candidate compound or drug, including antisense, on the informative array produced by the combination of Dooley et al. and Lockhart et al. with a reasonable expectation of success.

Response to Arguments:

Applicants' arguments rely on the teachings of Dooley et al. and Lockhart et al. which have been fully addressed above. Since Applicants do not make any new arguments herein, the rejection is maintained for the reasons of record herein.

The rejection of claims 28, 29, and 46 under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000) in view of Lockhart et al. (WO 97/10365, published March 20, 1997) as applied to claims 1-13, 15-24, 26, 27, 30-45, and 47-50 above, and further in view of Nilsen (U.S. Patent No.

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6,046,038, issued April 4, 2000) and Shuber (U.S. Patent No. 5,882,856, issued March 16, 1999), made in the Office Action mailed on August 22, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on March 30, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Preliminarily, claims 28-30 and 46 are multiple dependent claims, depending directly or indirectly from independent claims 1 and 25. The rejection of claims under this section is based on their dependency on claim 1.

The teachings of Dooley et al. and Lockhart et al. have already been discussed above.

Dooley et al. and Lockhart et al. do not disclose a method of amplification involving multiplex PCR (claim 28), use of universal priming sequence (claim 29).

Dooley et al. and Lockhart et al. do not disclose a method of signal amplification involving one or more of BDA, RCA, HSAM, RAM, and DNA dendrimer probe (claim 46).

Shuber discloses a multiplex amplification procedure involving the use of gene specific primers comprising a universal sequence (column 2, lines 54-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the multiplex amplification method employed by Shuber in the amplification step of Dooley et al. and Lockhart et al. for the motivation/advantage of simultaneously generating amplicons of multiple target nucleic acids which is known in the art as reducing time, contamination as well as reagent costs.

Nilsen discloses a method of detection involving DNA dendrimer probe (Figures 1A and 1B; column 9, lines 20-25).

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Nilsen discloses that the use of dendrimer probe comprises arms organized at a surface layer with the capacity to bind the target as well as multiple labels, *which results in amplified signal* (column 9, lines 21-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, to combine the teachings of Nilsen with the teachings of Dooley et al. and Lockhart et al. for the advantage of amplifying the signal produced by the target probe employed by Dooley et al. and Lockhart et al., achieving “50 to 100-fold signal enhancement,” (column 9, lines 62-63) the signal of which is critical in assays involving nucleic acid hybridization.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants’ arguments rely on the teachings of Dooley et al. and Lockhart et al. which have been fully addressed above. Since Applicants do not make any new arguments herein, the rejection is maintained for the reasons of record herein.

The rejection of claims 28-32, 35-36, and 46-49 under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (U.S. Patent No. 6,635,423 B2, issued October 21, 2003, filed January 16, 2001, priority January 14, 2000) in view of Lockhart et al. (WO 97/10365, published March 20, 1997) Nilsen (U.S. Patent No. 6,046,038, issued April 4, 2000) and Shuber (U.S. Patent No. 5,882,856, issued March 16, 1999), made in the Office Action mailed on August 22, 2005 is maintained for the reasons of record.

Applicants’ arguments presented in the Amendment received on March 30, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, “Response to Arguments” section.

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The Rejection:

Claims 28-32, 35-36, and 46-49 are multiple dependent claims, depending directly or indirectly from independent claims 1 and 25. The rejection of claims under this section is based on their dependency on claim 25.

The teachings of Dooley et al. have already been discussed above.

Dooley et al. do not disclose a method of amplification involving multiplex PCR (claim 28), use of universal priming sequence (claim 29), or pooling of amplification product (claim 30), wherein selective amplification amplifies between about 5 and about 100 polynucleotide sequences (claim 31), between about 10 and about 50 polynucleotide sequences (claim 32).

Dooley et al. do not disclose a method of employing housekeeping genes (claims 35 and 36).

Dooley et al. do not disclose a method of signal amplification involving one or more of BDA, RCA, HSAM, RAM, and DNA dendrimer probe (claim 46) or involving enzyme-ligand based detection (claims 47-49).

With regard to claims 28 and 29, Shuber discloses a multiplex amplification procedure involving the use of gene specific primers comprising a universal sequence (column 2, lines 54-60).

With regard to claim 30, Lockhart et al. disclose pooling (page 7, lines 10-12).

With regard to claims 31 and 32, depending on the number of the differentially expressed RNAs identified by the method of Dooley et al., the selective amplification would necessarily amplify between about 5 to about 100; or between about 10 and about 50 polynucleotide sequences.

With regard to claim 35, Lockhart et al. disclose the use of housekeeping genes for internal expression control (page 17, line 5; page 35, line 25 to page 36, line 5).

With regard to claim 36, the differentially expressed nucleic acid produced by treatment with a particular compound will necessarily be different the differentially expressed nucleic acid produced from a different compound (thus different second defined sequence probe). The use of housekeeping genes (or the first defined sequence probe) as an expression control, as demonstrated by Lockhart et al. will be same sequence however.

With regard to claim 46, Nilsen discloses a method of detection involving DNA dendrimer probe (Figures 1A and 1B; column 9, lines 20-25). Nilsen discloses that the use of dendrimer probe comprises arms organized at a surface layer with the capacity to bind the target as well as multiple labels, **which results in amplified signal**' (column 9, lines 21-23).

With regard to claims 47-49, Lockhart et al. disclose a method of detection involving enzyme and substrate (or ligand) (page 31, lines 21-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Dooley et al., Lockhart et al., Shuber et al., and Nilsen to arrive at the claimed invention for the following reasons.

With regard to the teachings provided by Lockhart et al., the use of housekeeping genes in an array for the purpose of quality control, enzyme-ligand based signal amplification, pooling of samples for arraying are techniques commonly practiced in the art of microarray technology so as to quality control the intensity of the hybridization patterns, as well as spotting nucleic acids on an array, rendering the combination obvious over Lockhart et al.

With regard to the teaching provided by Nilsen et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, to combine the teachings of Nilsen with the teachings of Dooley et al. and Lockhart et al. for the advantage of amplifying the signal produced by the target probe employed by Dooley et al. and Lockhart et al., achieving "50 to

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100-fold signal enhancement,” (column 9, lines 62-63) the signal of which is critical in assays involving nucleic acid hybridization.

With regard to the teachings provided by Shuber et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the multiplex amplification method employed by Shuber in the amplification step of Dooley et al. and Lockhart et al. for the motivation/advantage of simultaneously generating amplicons of multiple target nucleic acids which is known in the art as reducing time, contamination as well as reagent costs.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings as the various types of signal amplification methods provided for by Lockhart et al. (enzyme-ligand based) and Nilsen et al. (dendrimer) would not have conflicted with one another as they are well-known alternative methods of labeling nucleic acids in hybridization assays. Further more, the teachings of Shuber et al. would not conflict with the teachings of Lockhart et al. and Nilsen et al., and Dooley et al. in that the teachings of Shuber et al. is directed to amplification of nucleic acids which would not affect the labeling scheme taught by Lockhart et al., Nilsen et al. and Dooley et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants' arguments rely on the teachings of Dooley et al. and Lockhart et al. which have been fully addressed above. Since Applicants do not make any new arguments herein, the rejection is maintained for the reasons of record herein.

Conclusion

No claims are allowed.

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THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Inquiries

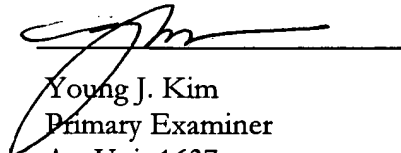
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the

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status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
Primary Examiner
Art Unit 1637
6/13/2006

yjk